

# Donor risk factors for delayed graft function in human kidney transplantation

Oliver Raatesalmi

Bachelor of Medicine

HUCH Meilahti hospital, OR, ICU and pain relief

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[oliver.raatesalmi@helsinki.fi](mailto:oliver.raatesalmi@helsinki.fi)

Minna Ilmakunnas

University of Helsinki

Faculty of Medicine

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Tiivistelmä - Referat – Abstract  <p>Suomessa tehdään vuosittain noin 240 munuaissiirtoa ja siirtojen määrä on kasvamassa. Verrattuna dialyysihoitoon munuaisensiirto antaa potilaalle pidemmän elinajanennusteen sekä paremman elämänlaadun. Munuaisensiirto on lisäksi kustannustehokasta dialyysihoitoon verrattuna.</p> <p>Suomessa suurin osa (85%) munuaissiirteistä tulee aivokuolleelta elinluovuttajalta. Loput siirteet tulevat eläviltä luovuttajilta, mutta maailmalla käytetään myös verenkierron pysähtymiseen menehtyneitä elinluovuttajia. Aivokuolema aiheuttaa elinluovuttajalle verenkierronsäätelyn häiriöitä sekä muutoksia immuuni- ja hyytymisjärjestelmiin. Lisäksi munuaissiirteen kylmä- ja lämminsäilytys sekä verenkierron palauttaminen aiheuttavat siirteelle iskemia-reperfuusio vaurion. Tämä voi aiheuttaa munuaissiirteen hidastuneen käynnistymisen (delayed graft function, DGF) aiheuttaen dialyysihoidon tarpeen. Munuaissiirteen hidastuneen käynnistymisen yleisyys Suomessa on tällä hetkellä noin 25%.</p> <p>Tässä tutkielmassa on analysoitu 100 munuaissiirtopotilaan muodostama aineisto. 89 munuaissiirteistä oli Suomesta ja 11 munuaissiirrettä saatiin Pohjoismaisen jakeluverkoston kautta. Munuaissiirrot on tehty vuosina 2015-2016. Tutkimuksen tavoitteena on selvittää, mitkä elinluovuttajaan liittyvät tekijät vaikuttavat DGF:n kehittymiseen.</p> <p>30%:lle aineiston potilaista kehittyi DGF. Tilastollisesti merkittäviä tekijöitä DGF:n kehittymiselle olivat elinluovuttajan BMI ja verenpainetauti. Tutkimus tuo vahvistusta jo aikaisemmin tiedossa olleille DGF:n riskitekijöille suomalaisessa aineistossa. DGF lisää munuaissiirtoon liittyviä kustannuksia ja huonontaa siirteen pitkäaikaisennustetta. DGF:lle altistavat tekijät ovat suurelta osin elinluovuttajaan liittyviä (64%). Tämä puoltaa ajantasaisten ja yhtenäisten elinluovuttajan hoito-ohjeiden käyttöä.</p>			
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## 1. Literature review

Kidney transplantation is the superior treatment for patients with end-stage renal disease that can withstand surgery and immunosuppressive medication. Kidney transplantation has proven to improve life quality and expectancy in addition to reducing health care costs compared to hemo- or peritoneal dialysis. Kidney transplantations are increasing in number and currently about 240 kidney transplantations are done yearly in Finland<sup>1</sup>. Most common causes of end-stage renal disease, and thus indications for kidney transplantation, in Finland include: diabetic nephropathy, pyelonephritis and polycystic kidney disease<sup>2</sup>. Common complications after kidney transplantation include delayed graft function (DGF), acute rejection and urologic complications.

### 1.1 Organ donors

Donation after brain death (DBD) is the principal donor type in Finland. In Finland, brain death is diagnosed through comprehensive neurologic assessment with absence of brain stem reflexes, followed by the apnea test. Also, the cause or pathophysiological mechanism of brain death has to be known. CT angiography might also be used in unclear situations<sup>3</sup>. In Finland over 85% of kidney grafts are from DBD donors and the rest are from living donors. The amount of living donor kidneys has been rising in recent years but is low compared to amounts worldwide (about 40%)<sup>1</sup>. Currently in Finland a relative or a person living in the same household can act as an organ donor.

If no such donor exists, any fully mentally competent adult can act as an organ donor. Transplantation results from living donors are better compared to DBD donors, because living donors are not affected by brain death induced changes and long cold ischemia time. Recent international registry studies reported DGF in approximately 26% of deceased-donor recipients and 3-5% in living-donor recipients<sup>4</sup>.

Globally due to organ shortage the use of marginal organs has increased. Extended criteria donors (ECD) refer to kidney grafts with a relative risk of 1.70 or more for graft failure compared with DBD donors<sup>5</sup>. Commonly used ECD donor characteristics are age over 60 years or age 50-59 with two of the following three criteria: history of hypertension, serum creatinine over 133  $\mu\text{mol/l}$  or death from cerebrovascular accident. ECD organs have a higher risk for DGF and rejection<sup>6</sup>.

Donation after circulatory death (DCD) is rising but is not used in Finland due to DBD organs supplying the demand. DCD organs do not suffer from injuries mediated by brain death but are affected by prolonged warm ischemia time during asystole and organ procurement. DCD kidneys have higher rates of DGF but might have similar long-term outcomes compared to DBD kidneys<sup>7</sup>.

## 1.2 Effects of brain-death

During brain death, ischemia in brainstem releases a burst of catecholamines to maintain cerebral perfusion pressure. This is often referred to as a catecholamine storm, characterised by higher cardiac output and vascular resistance leading to

hypertension. After sympathetic activation subsides and vasodilation occurs, the donor can become hemodynamically unstable. This can lead to compromised perfusion of organs, which can then lead to acidosis and elevated levels of lactate and glucose. These changes reflect a shift from aerobic to anaerobic metabolism<sup>8</sup>.

Regional vascular beds can autoregulate their perfusion and have different threshold blood pressures where their ability to do so weakens. The brains and coronaries appear to lose autoregulation between 30-50 mmHg mean arterial pressure (MAP), while the mammalian kidney loses autoregulation at approximately MAP 70 mmHg. After autoregulation is lost, the organ blood flow declines in a linear fashion as blood pressure falls. In patients with long history of hypertension or critical atherosclerosis, the fall is likely to occur at a higher blood pressure<sup>9,10</sup>. This could indicate that these donors should have higher MAP goals. Recommended MAP over 60-70 mmHg by many guidelines for the treatment of organ donor is not based on randomized controlled trials (RCT)<sup>11</sup>. MAP recommendations are based on general critical care guidelines.

Use of catecholamines to maintain donor blood pressure is widely used, but they should be administered at low doses. Catecholamines raise blood pressure by vasoconstriction, which could cause renal artery vasoconstriction and decrease renal blood flow in hypotensive patients. In a 2004 multicenter RCT, low-dose dopamine was confirmed to improve immediate graft function after kidney transplantation in DBD donors. In kidneys with cold ischemia time (CIT) over 17h the beneficial effect was enhanced<sup>12</sup>. the beneficial effects of dopamine have been proposed to be due to more stable hemodynamics and poorly

known cytoprotective effects. RCTs comparing different vasoactive drugs are lacking<sup>11</sup>.

During brain death, the hypothalamic-pituitary axis ceases to function which effects systemic hormone levels. Reduction of vasopressin levels leads to diabetes insipidus, worsening hypovolemia and hemodynamic stability. Desmopressin, a synthetic analog of vasopressin, is widely used in organ donor care to maintain fluid balance and hemodynamics. Declining thyroid hormone levels can affect cellular metabolism, causing acidosis. Thyroid hormones can also be linked to the decline of cardiocirculatory function, but studies have failed to show thyroid hormone therapy to improve kidney function post-transplantation. Cortisol is an anti-inflammatory hormone and declining levels can aggravate inflammation and immunologic activation in the donor. Treating kidney donors with steroids might improve outcomes after transplantation. Steroid treatment has been shown in experimental kidney transplantation settings to reduce rejection rates, inflammatory cell infiltration and have improved graft survival<sup>8</sup>.

Brain death has notable effects on inflammatory responses and immune activation. Complex interactions between vascular endothelium, the complement and coagulation system are behind inflammatory events of brain death. Endothelial activity facilitates cell migration enabling location of inflammatory cells. complement factor levels have been studied in kidneys from brain dead donors and increased C3-levels shown to correlate clinically with worse renal transplant function<sup>8</sup>.

Thromboplastin is released in cerebral damage. This starts fibrin clotting through the extrinsic pathway. Also, enhanced systemic



platelet activation has been observed. Blood clots can cause damage by blocking microcirculation and causing tissue hypoxia. Cytokine levels are higher in cadaver donors compared to living donors<sup>13</sup>. Antigen-independent (innate) immune system mediated injury occurs during brain death in the donor. It is thought to have enhanced or triggering effects on allograft rejection<sup>14</sup>. There has also been conflicting results in kidney inflammation after brain death, where kidney biopsies prior to organ retrieval showed no difference in major inflammatory markers compared to living donor kidneys<sup>15</sup>.

Organ donor care takes place at various hospitals and standards of care can vary. Diagnosis of brain death takes place substantially later than the pathophysiological effects on the body occur. This and getting research permits for brain-dead donors treatment interventions can lead to difficulties conducting research. One study reported that mild hypothermia 34-35 Celsius compared to normothermia in DBD donors reduced the rate of DGF (28% vs 39%) in a 370 organ donor study<sup>16</sup>. Hormonal resuscitation involving methylprednisolone, vasopressin and triiodothyronine/L-thyroxine was shown in a retrospective analysis of the United Network of Organ sharing (UNOS) database to increase organ yield and improve graft survival after 1 year<sup>6</sup>. Hormonal resuscitation might be more beneficial to hemodynamically unstable patients<sup>11</sup>. Organ donor vital care compared between UNOS and Finnish organ donor guideline is presented below in table 1. Hormonal resuscitation and vasopressors are compared in table 2.

Organ donor care	UNOS	Finnish organ donor care guideline
MAP, mmHg	60-100	≥ 60-65
Central venous pressure, mmHg	4-10	≤ 8
Arterial blood gas pH	7.3-7.45	7.35-7.45
PaO <sub>2</sub> :FiO <sub>2</sub>	>300	>300
Serum sodium, mmol/l	135-155	137-145
Blood glucose, mmol/l	< 8.3	5-8
Urine output, ml/kg/h	0.5-3	0.5-3

Table 1. Organ donor vital care comparison between UNOS and Finnish organ donor care guideline<sup>17,18</sup>.

Hormonal resuscitation and vasopressors	UNOS	Finnish organ donor guideline	Eurotransplant	NHS guideline
<b>Vasopressors</b>	one vasoactive and low dose (dopamine ≤10 µg/kg/min, phenylephrine ≤60 µg/kg/min, noradrenaline ≤10 µg/kg/min)	dopamine 2-10 µg/kg/min	Dopamin 3-6 µg/kg/min or noradrenaline < 0.2 µg/kg/min, avoid adrenaline and phenylephrine	dopamine (preferred) or dobutamine if required
<b>Desmopressin</b>	consider in diabetes insipidus	0.2-0.8 µg if urine output > 3ml/kg/h	2-4 µg bolus if diuresis >5ml/kg/h	1-4 µg iv titrated to effect if diuresis >4ml/kg/h
<b>Vasopressin</b>	Vasopressin 1 unit bolus: 0.5-4.0 unit/h infusion	0.5-2 units/h	inotropic and vasopressive support	0.5-4 units/hour
<b>Methylprednisolone</b>	15mg/kg	1000mg	dosage not discussed	15mg/kg (max 1000mg)
<b>T3/T4</b>	T3 4µg bolus and 3µg/h infusion	by cardiac surgeon's demand: UNOS T3-protocol or T4 20µg bolus and 10 µg/h infusion	-	-

Table 2. Hormonal resuscitation and vasopressors compared with UNOS<sup>6,18</sup>, Finnish<sup>17</sup>, Eurotransplant<sup>19</sup> and NHS<sup>20</sup> guidelines.

### 1.3 Ischemia-Reperfusion injury

During organ procurement, preservation and transplantation the kidney graft is affected by various damaging mechanisms. Prior to this, grafts from DBD donors have been influenced by the damaging effects of brain death. After procurement the graft is flushed with preservation solution and cooled to 4 degrees Celsius. This stage is referred to as cold ischemia. During transplantation the kidney is removed from the preservation solution to perform vascular anastomoses, and this time prior to opening of vessels is referred to as warm ischemia. Opening the circulation into the graft initiates reperfusion. Damage from these different stages is referred to as ischemia-reperfusion (IR) injury.

During cold ischemia, hypoxia damages endothelial cell function, increasing vascular permeability and causing transcriptional reprogramming. Hypoxia damages mitochondria and accelerates the production of oxygen radicals. Oxygen radicals disrupt intracellular metabolism and cause damage to cell membranes. Hypoxia also activates cell death programs and necrotic cells produce cytokines leading to inflammation.

Declamping of the vessels initiates reperfusion, enabling the activation of innate and adaptive immune responses, causing an influx of cells leading to vascular congestion, activation of the complement, clotting cascades and thrombosis. Combined, this microvascular dysfunction can result in a no-reflow phenomenon in capillaries where, despite adequate macrovascular perfusion, microvascular perfusion is insufficient for tissue oxygen delivery. Dendritic cells may launch direct allorecognition in kidney injury. Dendritic cells present antigens

to recipients T cells, initiating the activation of adaptive immune system<sup>21,22</sup>. IR injury may culminate in DGF, leading to greater graft immunogenicity predisposing the allograft to acute and chronic rejection<sup>23</sup>.

#### 1.4 Delayed graft function definitions

DGF is most commonly defined as the requirement for dialysis within seven days of kidney transplantation. However, 18 different definitions for DGF can be found in literature mostly based on dialysis and/or creatinine levels<sup>24</sup>. This can complicate study comparison. Comparing graft function and survival with 10 different definitions of DGF showed that no definition was superior in predicting graft outcomes<sup>25</sup>. Different DGF definitions are presented below on Table 3<sup>25</sup>.

##### Dialysis-based

The requirement for dialysis in the first postoperative week
The requirement for dialysis in the first postoperative week excluding the first 24 hr
The requirement for two or more episodes of dialysis in the first postoperative week
The requirement for dialysis in the first 10 days postoperatively

##### Creatinine-based

Failure of a fall in serum creatinine of 10% on 3 consecutive days in the first postoperative week
Serum creatinine at postoperative day 7 $\geq 221 \mu\text{mol/l}$
Serum creatinine at postoperative day 10 $\geq 221 \mu\text{mol/l}$
Fall in ratio of creatinine of postoperative days 1 and 2 of at least 30%

##### Combination

Dialysis in first week or failure of creatinine to fall in first 24 hr
Dialysis in the first week or serum creatinine at postoperative day 7 $\geq 221 \mu\text{mol/l}$

Table 3. Different DGF definitions.

Defining DGF as the use of dialysis in the first postoperative week is most widely used and clinically feasible. It is also used in this study. As a downside, indications for dialysis post-operatively (e.g. hyperkalemia, fluid overload, uremia) can vary between centers and physicians. Postoperative graft function can also be influenced by acute rejection, infections and surgical complications. Biopsy should be considered after 10 days of impaired graft function<sup>4</sup>. Biopsy can differentiate between DGF and acute rejection. Nashan et al. showed that biopsy revealed the cause of impaired graft function to be acute rejection instead of DGF in 17% of cases<sup>4</sup>.

### 1.5 Delayed graft function risk factors

Risk factors for DGF can be attributed to different stages of the transplantation process. Firstly, donor factors play an important role. 64% of the variability in renal allograft function 6 months after transplantation can be attributed to the donor kidney<sup>26</sup>. After procurement the graft is predisposed to cold and warm ischemia followed by reperfusion. After reperfusion recipient factors affect graft outcome.

In the recent years, the usage of marginal organs (ECD and DCD) has increased the incidence of DGF. Current prediction models for DGF overestimate the incidence of DGF. DGF risk factors are presented in Table 4<sup>4</sup>. Vasoactives are compared in Table 5. RCTs comparing vasopressors are lacking and they are often used in combinations in donors. Vasoactive drugs are used to control brain death induced hemodynamic changes and improve organ perfusion. They can also decrease organ perfusion by increasing peripheral vascular resistance and

therefore low doses are recommended. Noradrenaline has shown mixed results in graft function and outcomes. In addition, the effects can be dose-dependent. No benefit for DGF prevention can be concluded from noradrenaline<sup>27,28</sup>, dobutamine<sup>29</sup> and phenylephrine<sup>29</sup> usage.

Donor	Recipient	Preservation and Immunology
Age	Male gender	Cold ischemia time
BMI	BMI	Warm ischemia time
Deceased vs living donation	Black race	HLA mismatches
Increasing donor serum creatinine	Duration of dialysis	
History of hypertension	Pretransplant blood pressure	
ECD and DCD donors	Previous transplant	
Diabetes	Diabetes	

Table 4. Donor risk factors for DGF.<sup>4</sup>

Vasoactives and Desmopressin	DGF
Low dose dopamine 4 µg/kg/min	Decreases DGF incidence, Improves graft survival if CIT > 17 h <sup>12</sup>
Desmopressin	No difference in DGF but might improve graft survival <sup>6,30</sup>
Vasopressin	No effect on DGF, increases organ yield <sup>31</sup>
Noradrenaline	Might improve graft survival and reduce graft rejection <sup>27,28</sup>
Phenylephrine, adrenaline, dobutamine	Generally recommended in severe shock. <sup>29</sup>

Table 5. Vasoactives and Desmopressin effects on DGF.

### 1.6 Clinical significance of delayed graft function

In a 2008 meta-analysis DGF was associated with a 41% increased risk of graft loss at 3,2 years, 38% increase in the risk of acute rejection in the first year and resulted in higher serum creatinine concentrations at 3,5 years of follow-up. No difference was seen in patient survival at 5 years of follow-up<sup>32</sup>. DGF has detrimental effects on long-term graft survival, but maybe not on patient survival. As DGF eventually may lead to graft loss, it will cause patients to resume dialysis. The survival of patients is better with a transplanted kidney than that of patients on dialysis, which could lead to a difference in survival on patients who lost their graft. DGF is associated with higher risk of graft loss independently of acute rejection. DGF is linked to chronic allograft nephropathy which is likely responsible for the inferior graft survival<sup>4</sup>.

DGF is associated with prolonged hospitalization, higher transplantation costs and adverse effects on transplant recipients<sup>33,34</sup>. On average, patients with DGF were hospitalized for 10 days longer than those with early graft function<sup>34</sup>.

Organ transplantation provides a unique window of opportunity to treat only the organ. Organ donor studies have shown donor hypothermia<sup>16</sup>, low-dose dopamine<sup>12</sup> and shorter cold ischemia time<sup>35,36</sup> to reduce DGF. Also, guideline-based organ donor intensive care and hormonal resuscitation have increased organ yield. Machine perfusion, where the kidney graft is connected to a perfusion device and continuously pumped with a solution at temperatures 1-10 degrees Celsius, has been shown to decrease DGF incidence<sup>37,38</sup>.

## 2. Materials and methods

This study is a part of research project "Intra-graft coagulation events in clinical renal transplantation and delayed graft function" (ClinicalTrials.gov NCT02568696). The main object of this study is to assess which organ donor factors predispose to delayed graft function. Factors related to the graft recipient were not included in this study. 84 organ donors and 100 kidneys were included, consequently 16 donors donated both kidneys. Kidney transplants were performed during years 2015-16. All kidney transplants in Finland are performed at Helsinki University Hospital, Department of Transplantation and Liver Surgery. Kidney procurement was performed at various hospitals in Finland with a team from Helsinki University hospital



of transplantation. 11 kidneys were received through Nordic countries organ sharing network ScandiaTransplant.

Only patients having their first kidney transplanatation were accepted to the study. Prior to the kidney transplantation, patients were in hemodialysis or peritoneal dialysis. Immunosuppression was achieved with cyclosporin, methylprednisolone and mycophenolate mofetil. Patients with other immunosuppressant medications and patients with prior HLA-immunisation (PRA over 30) were excluded from this study. Also, patients that had used heparin or fondaparinux during the last two weeks before surgery for other indications than anticoagulation during hemodialysis were excluded.

HUS and the ethics committee approved this study (Dnro 64/13/03/02/2015). Data collected from patients is confidential and patient identification data was removed before data-analysis. Data collection started November 2017 and data-analysis was done in March 2019. Data was collected from the electronic medical record software and anesthesia, ICU and organ donor sheets.

The following data were recorded from organ donors: age, sex, weight, height, hypertensive disease, medications before ICU admission, multiorgan/kidney only donor, time of the declaration of brain death, and the cause of brain death.

From ICU stay, the following parameters were tracked: time of admission, history of hypotension (MAP <65 mmHg), urine output 12 hours before surgery, urine output during organ procurement, organ perfusion time and the use of dopamine, dobutamine, noradrenalin, adrenalin, phenylephrine,

vasopressin and desmopressin. Donor intensive care was carried out in accordance to Finnish treatment guide for organ donors<sup>17</sup>.

The latest available laboratory results from the ICU were used for creatinine, hemoglobin, thrombocyte count and thromboplastin time (PT). We were not able to get all the above-mentioned data from the 10 organ donors that were received through ScandiaTransplant. At least age, sex, BMI, cause of death and creatinine, ICU stay duration and desmopressin use were available from all donors. Clinical end points in this study were DGF and acute rejection during the three months follow up.

## 2.1 Statistical Analysis

Continuous data are expressed as medians with ranges, and categorical data as frequency with percentage. Statistical significance was tested with the non-parametric Wilcoxon and Mann-Whitney tests. Categorical data were tested with Pearson Chi-Square test, excluding the use of noradrenalin, which was tested with Fisher's exact test. Data are presented as median and range. The  $\alpha$ -level was 0.05 for all statistical tests.

## 3. Results

89 kidney donors were included in this study. 50 (60%) of donors were male and 34 (41%) female. Median age was 60 years (range 11 - 80). Median BMI was 25 kg/m<sup>2</sup> (range 18-40). Surprisingly, one donor had metformin medication even though usually donor diabetes is a contraindication to for kidney donation.

Causes of brain death are presented in Figure 1 and the distribution of donors in different hospitals in Figure 2, respectively.

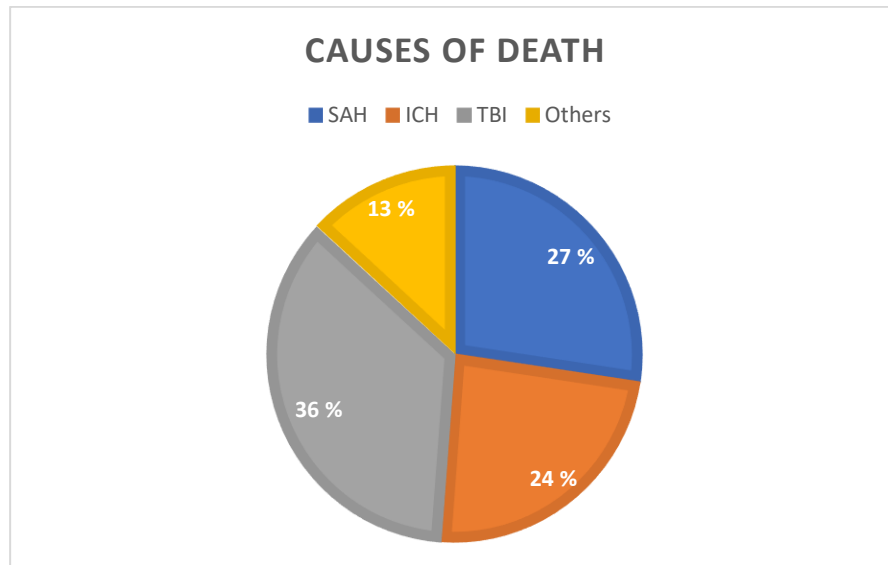


Figure 1. Donor causes of death. SAH = subarachnoid hemorrhage, TBI = traumatic brain injury such as subdural hematoma and others = meningitis, anoxia, stroke.

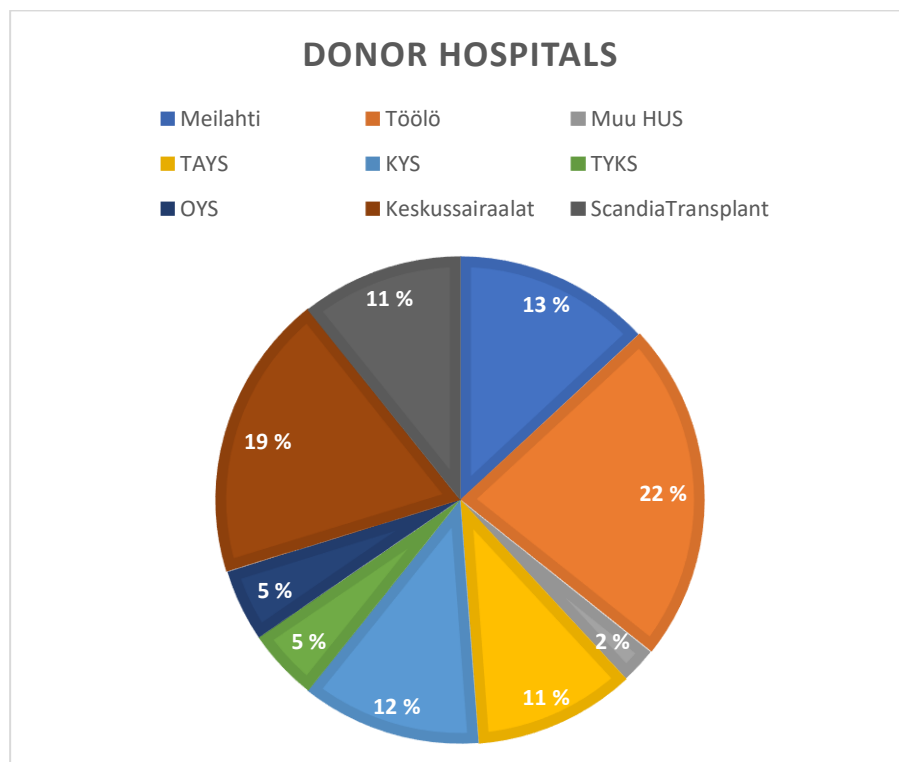


Figure 2. Donor hospitals presented with donor percentages.

45 (54%) of organ donors were multiorgan donors and 39 (46%) donated only one or two kidneys. 55 (65%) donors had hypertensive disease and 24 (29%) had not. 37 (44%) donors experienced hypotension (MAP <65 mmHg) during intensive care and 29 (35%) did not, data were missing from 18 (21%) donors.

### 3.1 Donor intensive care and laboratory tests

The median ICU stay was 36 hours (Table 6). ICU stay could not be calculated in 12 donors due to the lacking ICU admission time. The median time from brain death to organ procurement was 10 hours. Donor laboratory values prior to organ procurement are presented in Table 6.

	median with range
<b>ICU stay (days)</b>	1 (0-13)
<b>ICU stay (hours)</b>	36 (2-336)
<b>Time from brain death to organ perfusion (hours)</b>	10 (3-25)
<b>Creatinine (μmol/l)</b>	56 (32-99)
<b>Hemoglobin (g/l)</b>	120 (92-175)
<b>Thrombocyte count (x 10E9/l)</b>	182 (52-434)
<b>thromboplastin time (%)</b>	82 (9-152)
<b>Cumulative urine output 12 h before surgery (ml)</b>	1870 (540-4150)
<b>Cumulative urine output during organ procurement (ml)</b>	410 (69-2140)

Table 6. Donor ICU stay and laboratory values.

Vasoactive usage is presented in Table 7. None of the donors were treated with vasopressin and only one donor with adrenaline infusion. To treat diabetes insipidus, 66 donors received desmopressin and 18 did not.

Vasoactive	Yes	No	Missing data
<b>Noradrenaline</b>	73 (87%)	6 (7%)	5 (6%)
<b>Dopamine</b>	27 (32%)	48 (57%)	9 (11%)
<b>Dobutamine</b>	9 (11%)	66 (79%)	9 (11%)
<b>Phenylephrine</b>	17 (20%)	58 (69%)	9 (11%)

Table 7. Donor vasoactive usage.

### 3.2 Delayed graft function

Of the 100 donated kidney grafts, 30 (30%) developed DGF. Patients (recipients) were divided into DGF and no-DGF groups, and these two groups were compared regarding different donor factors. Donor BMI ( $p=0,019$ ) was statistically significantly different between the groups. In the DGF-group, BMI was slightly higher compared to no-DGF-group (Table 8).

	No DGF (n=70, 70%)	DGF (n=30, 30%)	p-value
<b>Age (years)</b>	60 (11-80)	60 (41-78)	0,322
<b>Creatinine (μmol/l)</b>	56 (32-99)	54 (36-99)	0,646
<b>BMI (kg/m<sup>2</sup>)</b>	25 (18-40)	26 (21-35)	0,019
<b>Time from brain death to organ perfusion (hours)</b>	10 (3-25)	9 (4-25)	0,575
<b>Cumulative urine output 12h before surgery (ml)</b>	1845 (650-4150)	1910 (540-3530)	0,479
<b>Cumulative urine output during organ procurement (ml)</b>	425 (70-1580)	380 (69-2140)	0,647
<b>ICU stay (days)</b>	1 (0-13)	1 (0-10)	0,064

Table 8. Continuous data presented with median and range.

Categorical data is presented in Table 9 and Figure 3. Donor hypertension was more common (p=0,046) in the DGF-group (Table 9).

	No DGF (n=70, 70%)	DGF (n=30, 30%)	p-value
<b>Male/female</b>	42 (66%) / 28 (78%)	22 (34%) / 8 (22%)	0,203
<b>Hypertension yes/no</b>	18 (56%) / 48 (76%)	14 (44%) / 15 (24%)	0,046
<b>Kidney/multiorgan donor</b>	35 (71%) / 35 (69%)	14 (29%) / 16 (31%)	0,760
<b>Hypotension yes/no</b>	32 (67%) / 25 (74%)	16 (33%) / 9 (26%)	0,506
<b>SAH/ICH/TBI/other</b>	19 (68%) / 20 (87%) / 22 (61%) / 9 (69%)	9 (32%) / 3 (13%) / 14 (39%) / 4 (31%)	0,206

Table 9. Categorical data compared with no DGF and DGF groups.

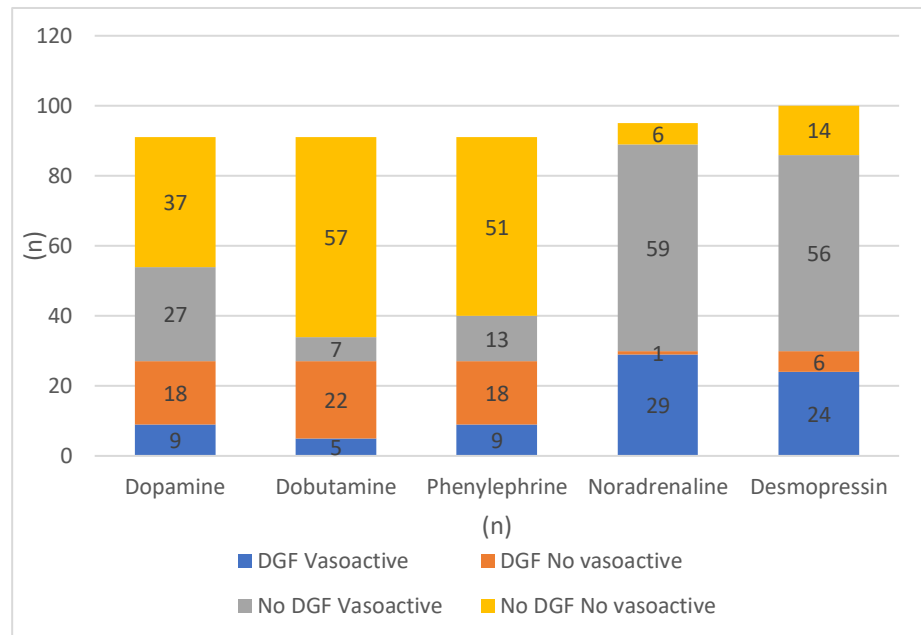


Figure 3. Frequency (n) of vasoactive agent and desmopressin use in DGF and no-DGF groups. No Vasoactive affected DGF statistically significantly. Dopamine  $p=0,430$ , Dobutamine  $p=0,329$ , Phenylephrine  $p=0,185$ , Noradrenaline  $p=0,426$ , Desmopressin  $p=1,00$ .

## 4. Discussion

30 (30%) of all patients developed DGF. The incidence of DGF in large international registry studies has been around 25%, indicating our results are in accordance with previous studies<sup>4</sup>. In this study, donor BMI predisposed to DGF, although the difference in the median BMI between DGF and no-DGF -groups was minimal. Donor BMI is a widely acknowledged DGF risk factor in earlier studies. Weissenbacher et al<sup>39</sup> showed donor BMI to correlate with the incidence of DGF. In their study, normal donor BMI 18.5-24.9 kg/m<sup>2</sup> resulted in 31% DGF and BMI more than 30 resulted in 51% DGF. Obesity can be associated with a proinflammatory state which could lead to a greater immunological response during IR-injury<sup>40,41</sup>. Further research is needed to validate this hypothesis in organ donors.

In this study, donor hypertension also proved to be a statistically significant risk factor for DGF. Hypertension can lead to hypertensive nephrosclerosis, resulting in a slowly decreasing kidney function with proteinuria and electrolyte imbalances<sup>42</sup>. Donor kidneys with histological changes due to hypertension have a higher risk for DGF and worse 1-year graft function<sup>43</sup>. Despite this, Akinlolu et al. showed that a kidney graft from ECD donor with hypertension gave the recipient 8,5 projected extra life years compared to staying on dialysis<sup>44</sup>. Thus, kidney transplantation, compared to staying on dialysis, improves life expectancy even with donor hypertension as a risk factor for DGF and chronic allograft nephropathy.

The type of brain death had no impact on DGF in this study. Some studies have reported non-traumatic brain death to be associated with DGF<sup>45,46</sup>. This might be due to poorer cardiovascular health in subarachnoid and intracranial hemorrhage patients.

Donor creatinine, age and diabetes are known risk factors for DGF<sup>4</sup>. Diabetic donors are not generally accepted for kidney donation in Finland. Donor creatinine and age were not statistically significant predictors of DGF in this study. This might be due to the low number of donors. Also neither donor gender, hypotension or multiorgan versus kidney only donation correlated with DGF.

Jushinskis et al<sup>47</sup> showed that severe hemodynamic disturbances in the donor (asystole or hypotension with systolic pressure < 90 mmHg) can predispose the kidney graft to DGF. In this study, however, hypotension (defined as MAP < 65 mmHg) did not predispose to DGF.



Vasoactive agents showed no correlation with DGF in this study. Protective effects of dopamine have been previously reported and dopamine treatment is part of the Finnish organ donor guideline<sup>12,17</sup>. Still, dopamine was used in only 32% of donors, compared with noradrenaline used in 87% of donors. In our material, vasoactive use varied and combinations were used. This shows that treatment protocols can vary between different hospitals despite national treatment guidelines. Due to the different treatment protocols and low statistical power, our findings on vasoactive use seem inconclusive.

Urine output is used as a clinical sign of kidney function and fluid status. Reduced urine output reflects impaired kidney function or dehydration. In the donor, increased urine output implies diabetes insipidus or excess fluid resuscitation. In this study, the cumulative urine output during organ procurement and 12 hours prior organ procurement had no effect on DGF. However, in 19% of the donors diuresis was unknown due to inadequate donor information. Urine output is a part of UNOS donor management goals and achieving these goals can reduce DGF incidence up to 50%<sup>48</sup>.

In conclusion, 30 (30%) patients developed DGF, which is comparable to international registry studies. In this study, only donor BMI and hypertension were statistically significant risk factors for DGF. Traditional risk factors such as donor age were not significant in this material. Finnish treatment guidelines were not followed regarding vasoactive use. Noradrenaline did not predispose the graft to DGF, therefore it seems to be a safe option when donor needs vasoactive support.

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